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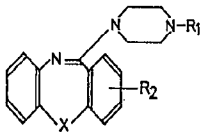
(54) NOVEL 11-[PIPERAZINYL]DIBENZ[B,F] [1,4] OXAZEPINES AND ANALOGOUS THIAZEPINES

(71) We, AMERICAN CYANAMID COMPANY, a corporation organised and existing under the Laws of the State of Maine, United States of America, of Berdan Avenue, Township of Wayne, State of New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new 11-[piperazinyl] dibenz[b,f] [1,4]oxazepines and thiazepines, to methods for the preparation of these new compounds, and to their use in pharmaceutical preparation.

The oxazepine and thiazepine compounds of this invention may be illustrated by the formula:



(I)

wherein X is oxygen or sulfur; R_1 is hydrogen, (C_1—C_4) alkyl or hydroxy (C_1—C_4) alkyl, and R_2 is cyano, di-(C_1—C_4) alkyl-sulfamoyl, (C_2—C_5) alkanoyl, α-chlorovinyl or (C_1—C_4) alkoxy-carbonyl, together with their non-toxic therapeutically useful acid addition salts.

The compounds of the present invention possess valuable central nervous system (CNS) properties at non-toxic doses. As such, they show one or more of the following CNS actions: tranquilizer, hypnotic and/or muscle relaxant type actions or anti-depressant actions. The compounds have been tested pharmacologically and found to have the above properties which show a desirable wide spread between doses producing depressant or anti-depressant actions and toxic symptoms such as paralysis or lethality. They are also analgesics.

The CNS depressant properties, such as tranquilizer, hypnotic and muscle relaxant type activity, are indicated by several procedures. For example, a test which indicates hypnotic and/or muscle relaxant type activity is represented by the following

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rod walking test. Groups of 6 mice each are tested for their ability to walk across a horizontal rod in a normal manner after receiving graded intraperitoneal doses of a test compound. A medium effective dose, rod walking dose (RWD) is estimated.

A test which indicates tranquilizing activity is represented by a measure of the reduction in motor activity. One-half of the rod walking dose (RWD); see above, is given to a group of 5 mice and a 5 minute count of motor activity is recorded (actophotometer). Counts of $\leqslant 250$ are considered to indicate a specific reduction (more than two standard deviations) of activity at a dose causing only minimal impairment of neurological function as measured by rod walking ability. Compounds that appeared to reduce motor activity ($\leqslant 250$ count) are administered to additional groups of 5 mice at graded doses and tested similarly. The motor depressant dose (MDD) which causes a 50% reduction of motor activity (A count of 250) is estimated. The use of reduced motor activity as a measure of tranquilizing activity has been described by W. D. Gray, A. C. Osterberg and C. E. Rauh, Archives Internationales et de Therapie, Vol. *134*, p. 198 (1961) and by W. J. Kinnard and C. J. Carr, Journal of Pharmacology and Experimental Therapeutics, Vol. *121*, p. 354 (1957).

When tested by the above procedures, representative compounds of this invention show activity indicated in the following table:

TABLE

Compound	MDD mg./kg. i.p.	RWD mg./kg. i.p.
2-dimethylsulfamoyl-11-(4-methyl-1-piperazinyl)-dibenz[b,f] [1,4]oxazepine	0.3	8.8
2-acetyl-11-(4-methyl-1-piperazinyl)-dibenz[b,f] [1,4]oxazepine	0.1	1.4
2-(α-chlorovinyl)-11-(4-methyl-1-piperazinyl)-dibenz[b,f] [1,4]ozazepine	0.9	10
2-dimethylsulfamoyl-11-(4-methyl-1-piperazinyl)-dibenzo[b,f] [1,4]thiazepine	8.3	>100
2-ethoxycarbonyl-11-(4-methyl-1-piperazinyl)-dibenz[b,f] [1,4]oxazepine	13	100

The anti-depressant properties of the compounds of the present invention are evident by measuring their ability to counteract a depression induced in animals by the administration of tetrabenazine hexamate. Graded doses of the active compounds of this invention are administered to groups of mice, and this is followed by administering a dose of tetrabenazine which is known to markedly depress the exploratory behaviour of normal mice. The anti-depressant treated groups show normal exploratory behaviour, while the control groups, and groups treated with an ineffective anti-depressant agent, do not show this normal exploratory behaviour, but show the well known profound depression induced by tetrabenazine. The results from several dose levels are used to establish effective dose ranges. The anti-depressant compounds of this invention show their desirable properties by this procedure at dose levels which produce little or no untoward reactions such as ataxia.

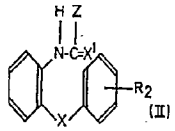
In addition, some of the new compounds of this invention show other valuable pharmaceutical properties such as analgesic activity.

The compounds of this invention are, in general, white crystalline solids only slightly soluble in water, but moderately soluble in organic solvents such as methanol and ethanol. They are basic substances which are usually soluble in aqueous mineral acids at room temperature. They form substantially insoluble acid addition salts such as the hydrochloride, sulfate, phosphate, citrate, tartrate, maleate and fumarate. The present compounds, generally in the form of their salts, may be administered orally or parenterally and when so administered are effective central nervous system agents. For oral administration, the new compounds of this invention may be incorporated with the usual pharmaceutical excipients and used, for instance, in the form of tablets, capsules, dragees, liquids to be administered in drops, emulsions, suspensions and

syrups, and in chocolate, candy and chewing gum. They may also be administered in suppositories, and in aqueous solutions for parenteral injection.

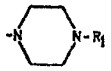
The new 11-aminodibenz[b,f][1,4]oxazepine and thiazepine compounds of this invention may be prepared by a number of general methods, two of which are as follows:

1. By (a) cyclizing a compound of the formula:



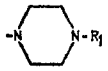
(II)

wherein X′ is sulfur or oxygen, Z is



or OH, halogen, OSO_2Ar, SH, SR, amino or substituted amino, wherein R_1, R_2 and X are as defined above, R is alkyl and Ar is aryl; and

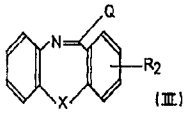
(b) when required, before or after cyclization, converting Z from OH, halogen, OSO_2Ar, SH, SR, amino or substituted amino, into



and

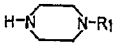
(c) when required, forming a non-toxic acid addition salt.

and 2. By (a) reacting a compound of the formula



(III)

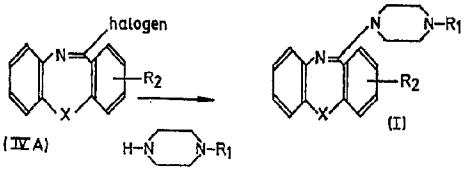
wherein Q is halogen, OH, OSO_2Ar, SH, SR, amino or substituted amino, wherein R is alkyl, Ar is aryl, and R_2 is as defined above, with a compound of the formula:



wherein R_1 is as defined above, and recovering the piperazine compound therefrom, and

(b) when required, forming a non-toxic acid addition salt.

A preferred method for preparing the compounds of this invention involves reacting an 11-halodibenz [b,f] [1,4] oxazepine or thiazepine with piperazine or a piperazine derivative, as follows:

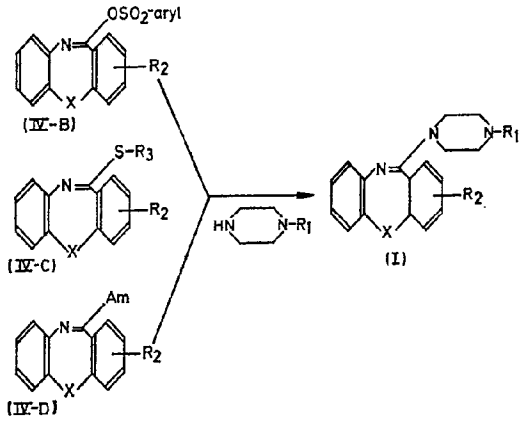


wherein X, R_1 and R_2 are as previously defined.

The reactive intermediates (IV—A) may be prepared by Beckmann rearrangements of substituted xanthone or thiaxanthone oximes in the presence of phosphorus

halides. Alternately, a substituted dibenz[b,f][1,4]oxazepine-11(10*H*)-one or dibenzo-[b,f][1,4]thiazepine-11(10*H*)-one may be converted to (IV—A) with phosphorus halides or thionyl halides. The reactive halogen intermediates (IV—A) may be isolated or, more conveniently, are prepared *in situ* and reacted with a piperazine without isolation. Suitable piperazines include N-methylpiperazine, piperazine and 1-(2-hydroxyethyl)-piperazine. This reaction is generally carried out in an inert solvent such as, for example, benzene, toluene, ether, tetrahydrofuran or chloroform. The reaction frequently proceeds spontaneously at room temperature, but the temperature may range from about 0°C. to about 150°C. It is usually complete within several hours.

The following equations represent further applications of general method (2):

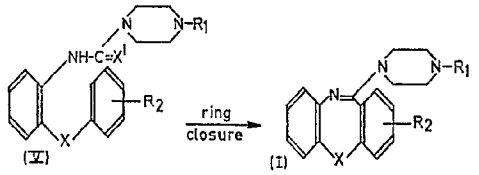


wherein X, R_1 and R_2 are as previously described, Am is amino, (C_1—C_4) alkyl amino or di-(C_1—C_4) alkylamino, and R_3 is hydrogen or alkyl. The 11-thio intermediates illustrated by (IV—C) may also be replaced by reactive 11-alkylsulfonyl groups or 11-arylsulfonyl groups which are capable of displacement by primary and secondary amines.

Transamination is generally carried out in the presence of an excess of the required piperazine in order to ensure an effective transamination in a reasonable period of time. The reaction is catalyzed by addition salts of the 11-aminodibenz[b,f][1,4]-oxazepine or thiazepine reactants which are generally employed in the proportions from about 0.1 to about 1.1 molecular equivalents. These salts may be prepared independently for use in the transamination reaction, or may be produced *in situ* during the reaction process. Suitable addition salts are those formed with acids such as hydrochloric, sulfuric and phosphoric. Mineral acid salts of piperazines, in limited amounts, are also useful catalysts in that they may be expected to produce salts of the 11-amino-benz[b,f][1,4]oxazepine reactants (IV—D) by an exchange process, and thereby facilitate the transamination process. Ammonium halides such as sodium chloride are also effective catalysts for the desired transaminations for the same reasons. These transamination reactions are generally carried out at temperatures of between 80°C. and 220°C. with the preferred temperature being from about 125°C. to 175°C. These reactions are frequently carried out at the refluxing temperature of the piperazine, which also acts as the solvent. The addition of other solvents which are inert under the reaction conditions may also be useful, such as alkanols and alkanol ethers, for example, ethanol, butanol and diethyleneglycol monoethyl ether. When effective transamination has been achieved, usually after heating from about 2 to about 48 hours, the desired products (I) are generally obtained by evaporation of the solvent and/or excess reagent, followed by purification of the crude product residue by methods well known to those skilled in the art.

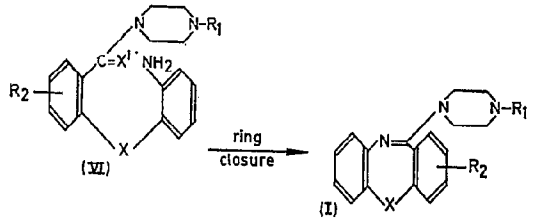
Another preparation of the compounds described in this invention from the 11-Am-intermediates IV—D where Am is amino comprises reacting this intermediate with a suitable N,N'-bis(2-chloroethyl)amine, including N,N-bis(2-chloroethyl)methylamine and N,N-bis(2-chloroethyl)amine. Additionally, an 11-piperazine derivative (I; R_1=H) may be further transformed to other derivatives within the preferred embodiment. For example, alkylation of I, R_1=H with (C_1—C_4) alkyl halides, and treatment of I, R_1=H with alkylene oxides are useful methods. Preparation of the 11-piperazinyl derivatives (I; R_1=H) may also be effected by removal of a suitable blocking group such as benzyl, carbalkoxy or carbobenzyloxy.

General method (I) above is illustrated by the following equation:



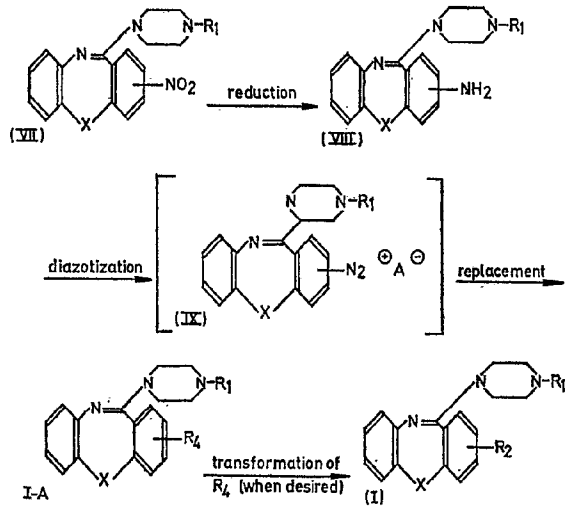
wherein X, X', R_1 and R_2 are as previously defined. By this method, compounds of Formula V are treated with condensing agents such as phosphorous oxychloride, phosphorus pentachloride, phosphorus pentoxide, polyphosphoric acid, zinc chloride and aluminum chloride in the presence or absence of an inert solvent at a temperature from about 100°C. to about 150°C.

A still further general method for the synthesis of the new compounds of this invention is:



wherein X, X', R_1 and R_2 are as hereinbefore described. By this general method *o*-(*o*-aminophenoxy)benzamides, *o*-(*o*-aminophenylthio)benzamides, *o*-(*o*-aminophenoxy)-thiobenzamides or *o*-(*o*-aminophenylthio)thiobenzamides are treated with condensing agents such as phosphorus pentachloride, phosphorus oxychloride and phosphorus trichloride in a solvent to obtain the desired compounds.

Another useful process for the new compounds of this invention is illustrated by the following reaction scheme:



wherein X, R_1 and R_2 are as previously defined, R_4 is cyano, sulfinic acid ($-SO_2H$) or α-oximino (C_1—C_4) alkyl ($-\overset{\overset{NOH}{\|}}{C}-$alkyl), and A is an anion of a mineral acid. By this procedure, a nuclear substituted nitro derivative of an 11-(piperazinyl)dibenz-[b,f][1,4]oxazepine or thiazepine (VII) is reduced to the corresponding nuclear substituted amino derivative (VIII) by any one of several methods. Suitable procedures include catalytic hydrogenation and reaction with chemical reducing agents, including,

for example, stannous chloride. This reduction is generally carried out in a solvent at a temperature within the range of from about 0° to 100°C. The resulting nuclear substituted amine derivatives (VIII) may be isolated and purified by methods well known to those skilled in the art, or, optionally, may be prepared and further used in the diazotization and replacement reactions without isolation or purification.

The diazotization of the nuclear substituted amino derivatives, (VIII) is generally effected in the presence of a mineral acid (HA) such as hydrohalogen acids, sulfuric acid and phosphoric acid, by the addition of an alkali metal or alkaline earth metal nitrite. These diazotizations are generally carried out in water. Alternatively, the diazotization may be carried out by treating a mineral acid melt salt of the nuclear substituted amino derivative (VIII) with an alkyl nitrite in the presence of a (C_1—C_4) alkanol. The diazotizations are carried out at a temperature range from about −25°C. to about 25°C. The diazonium salts (IX) produced by these procedures are, generally, unstable and reactive intermediates. Consequently, they are usually reacted "in situ", carrying out the replacement reaction without isolation of intermediates. In some cases, however, isolation of a diazonium salt (IX), particularly in the presence of a stabilizing agent, such as fluoborate salts, or stannic and cuprous salts, is possible and desirable. In these cases, the diazonium salt (IX) is isolated from the diazotization reaction, and then further transformed by the replacement reaction.

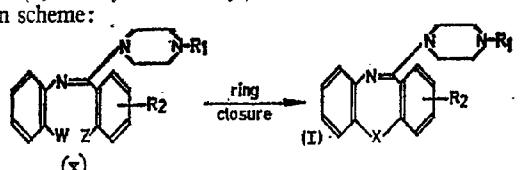
The diazonium salt replacement (to form the moiety R_2 in I) is then carried out with the suitable agent, followed by transformation of R_4 if required, to give the novel compounds of this invention (I). Preparation of the nitrile (I, $R_2 = CN$) is generally carried out with aqueous potassium cyanide in the presence of cupric or cuprous salts, nickel salts, or metallic copper. The reaction is generally performed in neutral to basic solution at temperatures from about 25° to 90°C.

Treatment of a diazonium sulfate or chloride IX with sulfur dioxide in the presence of copper powder yields the sulfinic acid (I—A, $R_4 = SO_2H$) which may be converted to the desired dilower alkyl sulfamoyl derivative [I, $R_2 = SO_2N(alkyl)_2$]. This diazonium salt replacement is generally effected by saturating the acidic solution of the diazonium salt at 0—25°C. with sulfur dioxide and then treating with copper powder until the reaction is complete. Alternatively, ferrous salts may be used for the reduction in the presence or absence of catalytic amounts of copper. The sulfinic acids (I—A; $R_4 = SO_2H$) are then oxidized with potassium permanganate or with barium peroxide to the corresponding sulfonic acid (I—A; $R_4 = SO_3H$) either in aqueous solution or in acetone at about 10—30°C. These sulfonic acids are also preparable directly from the diazonium salts by treatment of the salt with a solution of sulfur dioxide in aqueous acetic acid.

In either case, the sulfonic acid is then converted to the sulfonyl halide either by heating the sodium salt with phosphorus pentachloride or phosphorus oxychloride. Treatment of the resulting sulfonyl halide with an excess of the required dialkylamine then yields I; $R_2 = SO_2N(alkyl)_2$.

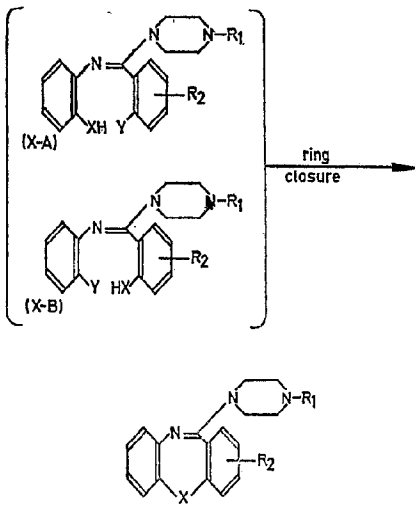
Reaction of the diazonium salt (IX) with (C_1—C_4) alkanol oximes yields oxime derivatives of 1—A; $R_4 = C(=NOH)$—alkyl. The diazonium salt is generally added to a cold solution of the oxime and the reaction is carried out at 0—15°C. and a pH *ca* 4.5 in the presence of a little sodium sulfite. The reaction generally requires one to several hours, and is considered completed when the reaction mixture no longer yields a color with naphthol. The resulting oxime is then isolated by methods well known to those skilled in the art and may then be hydrolyzed to the required ketone with either aqueous mineral acids, such as hydrochloric and sulfuric, or with the aid of a ketonic organic acid such as levulinic acid.

Still another process for the compounds of this invention comprises cyclization of substituted N-(1,N-diarylformimidoyl)diamine derivatives as illustrated by the following reaction scheme:



(x)

wherein R_1, R_2 and X are as defined hereinbefore and W and Z are reactive groups capable of effecting the ring closure whereby one of the W or Z groups is hydroxyl or mercapto and the other is a hydrogen, nitro, halogen or diazonium group. More specifically, an embodiment of this present process can be illustrated by the following ring closure reactions:



(I)

wherein R_1, R_4 and X are as previously defined, and Y is halogen or nitro. The ring closure reaction is achieved by heating the substituted N-(1,N-diarylformimidoyl)-piperazine [intermediates (X—A) or (X—B)] in an organic solvent. A polar solvent is generally employed to facilitate the reaction. Suitable solvents include formamide, dimethylformamide, dimethylacetamide, diethylacetamide and diethyleneglycol monoethyl ether. The ring closure is usually carried out at an elevated temperature, conveniently the refluxing temperatures of the solvent. Temperatures of from about 125°C. to about 200°C. are suitable, but the preferred temperature range is from about 150°C. to about 180°C. Heating is continued until the reaction is substantially complete, generally requiring from a few minutes to several hours or more.

An alkaline condensing agent may also be employed to promote ring closure in a reasonable period of time. Suitable condensing agents useful for these reactions are alkali or alkaline earth metal carbonates such as sodium carbonate, potassium carbonate, lithium carbonate and magnesium carbonate. Alkali metal hydroxides such as sodium hydroxide and potassium hydroxide may also be employed as alkaline condensing agents. Alkali metal hydrides and amides including sodium hydride and lithium amide, are also useful. These alkalis are generally used in approximately equivalent molecular portions with the N-(1,N-diarylformimidoyl)piperazine intermediates (X—A) and (X—B). A metal catalyst may also be, optionally, employed to facilitate the ring closure reaction. Copper powder is particularly useful, and copper salts are also successfully used.

The invention is illustrated by the Examples which follow. Examples 1, 2, 6 and 7 describe the preparation of intermediates employed in other of the Examples.

EXAMPLE 1

Preparation of *p*-(*o*-Aminophenoxy)acetophenone

A mixture of 27.8 g. (0.20 mole) of *p*-hydroxy-acetophenone, 31.5 g. (0.20 mole) of *o*-chloronitrobenzene, 27.6 g. (0.20 mole) of potassium carbonate and 0.2 g. of zinc-precipitated copper in 200 ml. of benzene is heated for about 4 hours under reflux. The reaction mixture is poured into 1 l. of water and stirred until a solid product separates. The solid is collected, washed with water (500 ml.) and then with petroleum ether (100 ml.) and dried in the air; *p*-(*o*-nitrophenoxy)acetophenone, melting point, 89—92°C., is thereby obtained. When recrystallized from 1:2 benzene-petroleum ether, this compound melts at 95—96°C.

Hydrogenation of a mixture of 12.5 g. of the above *p*-(*o*-nitrophenoxy)acetophenone and 100 ml. of ethanol in the presence of 0.1 g. of 10% palladium-on-charcoal is carried out until the theoretical amount of hydrogen is absorbed. The catalyst is removed by filtration, and the alcohol is evaporated under reduced pressure. The solid residue is recrystallized from ether-petroleum ether and *p*-(*o*-aminophenoxy)-acetophenone, melting point 70—71°C., is thereby obtained.

EXAMPLE 2

Preparation of *o*-(*p*-Dimethylsulfamoylphenoxy)aniline

A mixture of 56 g. (0.25 mole) of the dihydrate of sodium *p*-phenolsulfonate and 110 ml. of acetic anhydride is heated under reflux for 4 hours and concentrated to a solid. The solid is treated with 200 ml. of toluene and 60 g. of phosphorous pentachloride and refluxed for 1 hour. Concentration yields a mixture of solids containing *p*-acetoxybenzenesulfonylchloride.

This crude mixture is treated with 200 ml. of chloroform and filtered to remove salts. The filtrate is saturated at 0—10°C. with anhydrous dimethylamine for 4 hours (when loss of the enol acetate band at 5.65 μ was complete) and then filtered from dimethylamine hydrochloride. Concentration of the filtrate gives N,N-dimethyl-*p*-hydroxybenzenesulfonamide (somewhat contaminated with N,N-dimethylacetamide) as an oil. This oil is stirred with 40 g. of potassium carbonate in 200 ml. of dimethylformamide at 10°C. for 2 hours and then heated under reflux for 4 hours with 40 g. of *o*-chloronitrobenzene and 1 g. of zinc-precipitated copper. After standing overnight, the solvent is removed and the residue is triturated with 500 ml. of water to give solid N,N-dimethyl-*p*-(*o*-nitrophenoxy)benzenesulfonamide. Recrystallization from benzene-petroleum ether then gives material of melting point 111—112°C.

A mixture of 20 g. of the above nitroether, 60 g. of stannous chloride dihydride and 600 ml. of ether is stirred and treated cautiously with 20 ml. of concentrated hydrochloric acid at such a rate as to maintain gentle reflux. After stirring overnight, the aqueous layer is removed, treated with sodium bicarbonate to precipitate solids, and filtered. The solids are extracted thoroughly with 600 ml. of hot benzene. The benzene solution containing the desired amine is dried over potassium carbonate, filtered and concentrated to yield solid *o*-(*p*-dimethylsulfamoylphenoxy)aniline. When recrystallized from benzene-petroleum ether, this product melts at 152—155°C.; it may also be purified by sublimation.

EXAMPLE 3

Preparation of 2-Dimethylsulfamoyl-11-(4-methyl-1-piperazinyl)dibenz-[b,f][1,4]oxazepine

Crude *o*-(*p*-dimethylsulfamoylphenoxy)aniline (about 17 g.) in a mixture of 40 ml. of benzene and 100 ml. of petroleum ether is diluted with 50 ml. of pyridine and treated slowly with a solution of 30 g. of ethyl chlorocarbonate in 100 ml. of ether. The mixture is heated under reflux for 3 hours and concentrated. The residue on dilution with 400 ml. of water and filtering the solid, yields about 16 g. of ethyl *o*-(*p*-dimethylsulfamoylphenoxy)carbanilate, melting point 132—134°C. This compound melts at 134—135°C. when recrystallized from benzenepetroleum ether.

A mixture of 6 g. of the above carbanilate, 10 ml. of N-methylpiperazine and 40 ml. of benzene is heated under reflux for 5 days and then concentrated to dryness. The oily residue is suspended in 200 ml. of water and acidified with conc. hydrochloric acid. The resulting insoluble hydrochloride is collected, and recrystallized from methanol-ether. 2'-(*p*-dimethylsulfamoylphenoxy)-4-methyl-1-piperazinecarboxanilide hydrochloride, melting point 241—243°C., is thereby obtained and this product is satisfactory for use in the next step without further purification.

A mixture of 1.5 g. of the above salt, 4.0 g. of phosphorus pentoxide, and 20 ml. of phosphorus oxychloride is refluxed for 32 hours, cooled and poured onto ice. The product is extracted with chloroform after making the aqueous solution basic with concentrated ammonium hydroxide and dried over potassium carbonate. Concentration yields 1.4 g. of crude base which may be purified by adsorption chromatography on silica gel or, better, by partition chromatography on diatomaceous earth using a heptane-methanol solvent system. Concentration of the appropriate fraction of eluate (fifth hold-back volume) yields 2-dimethylsulfamoyl-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine, as a low-melting solid. This base is conveniently converted, with maleic acid in ethanol-ether, to the maleate salt, melting point 142—145°C. when recrystallized from acetoneether.

EXAMPLE 4

Preparation of 2-Acetyl-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine

A solution of 15 ml. of ethyl chlorocarbonate in 150 ml. of ether is added to a solution of 10 g. of *p*-(*o*-aminophenoxy)acetophenone in 100 ml. of chloroform at 0—10°C. followed by 15 ml. of pyridine. The mixture is refluxed for 2 hours and then concentrated. The residue is stirred with water for 30 minutes and then extracted with 150 ml. of ether. Drying over potassium carbonate, filtration and concentration then yields ethyl *o*-(*p*-acetylphenoxy)carbanilate as an oil suitable for use in the next

step; this product may be obtained as a solid, melting point 56—58°C., when crystallized from petroleum ether.

A mixture of 26 g. of the above carbanilate and 30 ml. of N-methylpiperazine containing a trace of sodium methoxide is heated at 100°C. for there days, and then refluxed for 4 hours and concentrated. The product is warmed with 400 ml. of 10% hydrochloric acid, filtered and the filtrate is made basic with potassium carbonate. The resulting 2'-(*p*-acetylphenoxy)-4-methyl-1-piperazinecarboxanilide melts at about 131—145° when recrystallized from benzene.

A mixture of 10 g. of the hydrochloride of the above 1-piperazinecarboxanilide (prepared from the base with hydrogen chloride in chloroform), 40 ml. of phosphorus oxychloride and 10 g. of phosphorus pentoxide is heated under reflux for 20 hr. and concentrated. The residue suspended in 400 ml. of ether is stirred with 200 g. of ice for 1 hour. The ether layer is isolated, dried over potassium hydroxide pellets, filtered and concentrated to give about 6 g. of a mixture of bases. These bases are separated by partition chromatography on an activated diatomaceous earth column by eluting with the upper phase of a mixture of methyl cellosolve and heptane while monitoring the ultraviolet absorption of the eluate at 240 mμ. Concentration of the fraction eluted at the 6th to 7th hold-back-volume gives 2-acetyl-11-(4-methyl-1-piperazinyl)dibenz-[b,f][1,4]oxazepine which melts at about 116—118°C.

Example 5

Preparation of 2-(α-Chlorovinyl)-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]-oxazepine

Concentration of another ultraviolet-absorbing fraction from the chromatogram described in Example 4, which is eluted at about the 5th to 6th hold-back-volume, yields 2-(α-chlorovinyl)-11-(4-methyl-1-piperazinyldibenz[b,f][1,4]oxazepine which melts at about 64—68°C.

Example 6

Preparation of *o*-(*p*-Dimethylsulfamoylphenylthio)aniline

To a solution of 125 g. of chlorosulfonic acid in 150 ml. of chloroform is added 87.5 g. (0.4 mole) of diphenyldisulfide drop by drop at 25—35°C. The mixture is stirred overnight, diluted with 500 ml. of chloroform and stirred with 400 g. of ice. After drying over sodium sulfate and chloroform solution is saturated with dimethylamine and stored overnight. Cooling to 0°C. and filtering gives 10 g. of 4-(N,N-dimethylsulfamoyl)diphenyldisulfide, melting point 132—136°C.

A mixture of the above disulfide (10 g.) and 10 g. each of zinc dust and ammonium chloride in 100 ml of ethanol with a few drops of water is stirred on a steam bath for 6 hours, diluted with 100 ml. of water and filtered. Concentration of the filtrate, addition of 100 ml. of water, and cooling to 0° gives colorless 4-mercapto-N,N-dimethylbenzenesulfonamide, m.p., 100—102°C. soluble in sodium hydroxide.

Reaction of this sulfonamide with *o*-nitrochlorobenzene in dimethylformamide containing potassium carbonate and a little copper powder, by the general method of Example 2, yields N,N-dimethyl-*p*-(*o*-nitrophenylthio)benzenesulfonamide. Reduction of this nitro compound with stannous chloride in a mixture of ether and hydrochloric acid then yields *o*-(*p*-dimethylsulfamoylphenylthio)aniline, melting point 120—122°C.

Example 7

Preparation of *p*-(*o*-Aminophenylthio)acetophenone

A mixture of 20 g. of *p*-bromoacetophenone and 12.5 g. of *o*-aminobenzenethiol is heated in 40 ml. of dimethylformamide in the presence of 14 g. of potassium carbonate. After 6 hours of refluxing, the reaction mixture is concentrated to dryness, and triturated thoroughly with 1 *N* sodium hydroxide. The insoluble fraction is dissolved in hydrochloric acid, washed with ether and precipitated with ammonium hydroxide to yield *p*-(*o*-aminophenylthio)acetophenone, melting point 78—80°C.

Example 8

Preparation of 2-Dimethylsulfamoyl-11-(1-piperazinyl)dibenzo[b,f][1,4]-thiazepine

o-(*p*-dimethylsulfamoylphenylthio)aniline (23.5 g.) is treated with 20 ml. of ethyl chlorocarbonate in benzenepyridine and heated under reflux for 2 hours. Bases are removed by extraction with hydrochloric acid, and the resulting benzene solution of ethyl *o*-(*p*-dimethylsulfamoylphenylthio)carbanilate is heated with carbethoxy piperazine containing a catalytic amount of sodium methoxide. 4-carbethoxy-2'-(*p*-di-

methylsulfamoylphenylthio)-1-piperazinecarboxanilide is thereby obtained. This 1-piperazinecarboxanilide (12 g.) is cyclized by boiling (for about 1 day) with a mixture of 20 ml. of phosphorus oxychloride and 12 g. of phosphorus pentoxide to give, after purification by partition chromatography, 2-dimethylsulfamoyl-11-(1-piperazinyl)-dibenzo[b,f][1,4]thiazepine, melting point 176—178°C.

EXAMPLE 9

Preparation of 2-Dimethylsulfamoyl-11-(1-piperazinyl)dibenz[b,f][1,4]oxazepine

About 45 g. of *o*-(*p*-dimethylsulfamoylphenoxy)aniline in 200 ml. of ether containing 50 ml. of pyridine is treated with 50 ml. of ethyl chlorocarbonate and refluxed for 2.5 hours. The reaction mixture is concentrated to dryness and the residue is washed with 300 ml. of water and with 200 ml. of dilute hydrochloric acid. The resulting ethyl *o*-(*p*-dimethylsulfamoylphenoxy)carbanilate has the melting point 132—134°C., when purified.

A mixture of 12 g. of the carbanilate, 20 g. of piperazine and 20 ml. of pyridine in 20 ml. of toluene is heated at 95—100°C. for 2 days and concentrated. The residue is extracted with 200 ml. of dilute hydrochloric acid and filtered. The filtrate is basified with potassium carbonate and extracted with chloroform. The solid hydrochloride of the resulting 2'-(*p*-dimethylsulfamoylphenoxy)-1-piperazine carboxanilide is precipitated with anhydrous hydrogen chloride.

This salt (12 g.) is heated with 20 g. of phosphorus pentoxide in 40 ml. of phosphorus oxychloride for 1 day and then poured into 400 g. of ice water. The oil precipitated with potassium carbonate is extracted with chloroform and the chloroform solution is extracted with 125 ml. of dilute hydrochloric acid. After clarifying with charcoal the aqueous layer is treated with potassium carbonate and resulting oil is subjected to partition chromatography to yield 2-dimethylsulfamoyl-11-(1-piperazinyl)-dibenz[b,f][1,4]oxazepine which melts at 187—189°C., when recrystallized from chloroform petroleum ether.

EXAMPLE 10

Preparation of 2-Dimethylsulfamoyl)-11-(4-ethyl-1-piperazinyl)dibenz[b,f][1,4]-oxazepine

2-Dimethylsulfamoyl-11-(1-piperazinyl)dibenz[b,f][1,4]oxazepine (Example 9) is treated with a slight excess of diethylsulfate in chloroform. When alkylation is complete, the reaction mixture is extracted with aqueous hydrochloric acid and the product is precipitated with ammonium chloride to yield 2-dimethylsulfamoyl-11-(4-ethyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine.

EXAMPLE 11

Preparation of 11-(4-Methyl-1-piperazinyl)-2-propionyldibenz[b,f][1,4]oxazepine

11-(4-methyl-1-piperazinyl)-2-nitrodibenz[b,f][1,4]oxazepine is dissolved in dilute hydrochloric acid and hydrogenated in the presence of palladium-on-charcoal to yield the corresponding 2-amino derivative.

The above 2-amino derivative is diazotized at 0—5°C., and then added to a neutralized solution of propionaldehyde oxime at about 25°C. in the presence of a little copper. When coupling is complete, the resulting 2-(α-oximinopropyl) derivative is extracted into acidic solution and this base is reprecipitated by treatment with ammonia. The crude product is further purified by dissolving it in sodium hydroxide solution and reprecipitating the base by the addition of ammonium chloride. This oximino derivative is then heated with levulinic acid to effect transoximination thereby yielding 11-(4-methyl-1-piperazinyl)-2-propionyldibenz[b,f][1,4]oxazepine which is isolated from the reaction mixture.

EXAMPLE 12

Preparation of 2-Acetyl-11-(1-piperazinyl)dibenzo[b,f][1,4]thiazepine

p-(*o*-aminophenylthio)acetophenone (Example 7) is treated with phosgene in *o*-dichlorobenzene and cyclized with aluminum chloride to give 2-acetyldibenzo[b,f]-[1,4]thiazepin-11(10H)-one. This compound is then heated with phosphorus pentachloride in toluene and the solvents are removed by distillation. The resulting 11-chloro derivative is heated with piperazine in toluene containing pyridine to yield the desired 2-acetyl-11-(1-piperazinyl)dibenzo[b,f][1,4]thiazepine.

EXAMPLE 13

Preparation of 2-Acetyl-11-(4-methyl-1-piperazinyl)dibenzo[b,f][1,4]thiazepine

The 11-piperazinyl derivative of the proceeding Example is heated with a mixture of formalin and formic acid to yield 2-acetyl-11-(4-methyl-1-piperazinyl)dibenzo-[b,f][1,4]thiazepine.

EXAMPLE 14

Preparation of 2-Acetyl-11-(1-piperazinyl)dibenz[b,f][1,4]oxazepine

The procedure of Example 12 is repeated using an equivalent amount of *p*-(*o*-aminophenoxy)acetophenone (Example 1) as starting material instead of *p*-(*o*-aminophenylthio)acetophenone. After suitable purification, 2-acetyl-11-(1-piperazinyl)dibenz[b,f][1,4]oxazepine is isolated.

EXAMPLE 15

Preparation of 2-Acetyl-11-[4-(2-hydroxyethyl)-1-piperazinyl]dibenz[b,f][1,4]-oxazepine

The product of Example 14 is treated with ethylene oxide in methanol to give 2-acetyl-11-[4-(2-hydroxyethyl)-1-piperazinyl]dibenz[b,f][1,4]oxazepine.

EXAMPLE 16

Preparation of 2-Dimethylsulfamoyl-11-(4-methyl-1-piperazinyl)dibenzo[b,f][1,4]-thiazepine

The procedure for Example 8 is repeated. When N-methylpiperazine is substituted for piperazine in the second step, 2′-(*p*-dimethylsulfamoylphenylthio)-4-methyl-1-piperazine carboxanilide is obtained, melting point 151—152°C. The procedure of Example 8 is continued; 2-dimethylsulfamoyl-11-(4-methyl-1-piperazinyl)dibenzo[b,f][1,4]-thiazepine melting point 162—165°C. is isolated as the desired end product.

EXAMPLE 17

Preparation of 3- (and 2) Cyano-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]-oxazepine

2-chloro-4-nitrobenzoic acid dissolved in tetrahydrofuran is treated with carbonyldiimidazole and heated until evolution of carbon dioxide is complete. The resulting solution is treated with *o*-aminophenol to yield 2-chloro-2′-hydroxy-4-nitrobenzanilide. This anilide is cyclized with potassium carbonate in dimethylformamide to give 3-nitrodibenz[b,f][1,4]oxazepin-11(10H)-one. Treatment of this intermediate with phosphorus pentachloride followed by N-methylpiperazine, as in Example 9, then gives 3-nitro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine.

This 3-nitro compound is reduced and diazotized, using the identical procedure described for the 2-isomer in Example 11, and the resulting 3-diazo derivative is treated with cuprous chloride in hydrochloric acid to yield. 3-cyano-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine.

When 2-nitro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine is similarly reduced, diazotized and treated with cuprous chloride in hydrochloric acid, the product is 2-cyano-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine.

EXAMPLE 18

Preparation of 2-Ethoxycarbonyl-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]-oxazepine

A mixture of 31 g. of *o*-chloronitrobenzene, 33 g. of ethyl *p*-hydroxybenzoate, 30 ml. of pyridine, 15 g. of potassium carbonate and 10 ml. of dimethylacetamide is refluxed for 7 hours and then poured into 800 ml. of dilute hydrocholric acid. The resulting oil is extracted with 500 ml. of benzene and concentrated to a solid. Washing with petroleum ether yields solid ethyl *o*-(*o*-nitrophenoxy)benzoate suitable for reduction.

The above ester in 250 ml. of ethanol is treated with 53 g. of ammonium chloride, 100 ml. of water, 20 ml. of conc. hydrochloric acid and 65 g. of zinc dust. After heating at 95—100° overnight, the basic reaction mixture is diluted with 380 ml. of water, cooled to 10° and filtered. The resulting solid is extracted with 250 ml. of chloroform which is dried over potassium carbonate and then concentrated to yield solid ethyl *p*-(*o*-aminophenoxy)benzoate.

This amino ether is then treated with ethyl chlorocarbonate and then with N-methylpiperazine by the procedure described in Example 5 to give 2′-(*p*-ethoxycarbonylphenoxy)-4-methyl-1-piperazinecarboxanilide. This compound is converted to the hydrochloride with anhydrous hydrogen chloride in chloroform, and the salt (10 g.) is refluxed with 10 g. of phosphorus pentoxide in 35 ml. of phosphorus oxychloride for 1 day. The mixture is treated with 200 ml. of ethanol and concentrated to dryness. The residue in 200 ml. of ether is washed with 250 ml. of water. The acidic aqueous layer is treated with concentrated ammonium hydroxide and then extracted with ether. Concentration of the ether yields the crude base which, when recrystallized twice from

ether-petroleum ether, gives 2-(ethoxycarbonyl)-11-(4-methyl-1-piperazinyl)dibenz-[b,f][1,4]oxazepine, melting point 109—111°C.

EXAMPLE 19

Preparation of 2-Dimethylsulfamoyl-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]-oxazepine

o-(*p*-Dimethylsulfamoylphenoxy)aniline (Example 2) is treated with phosgene in *o*-dichlorobenbenzene and cyclized with aluminum chloride to give 2-dimethylsulfamoyldibenz[b,f][1,4]oxazepine-11(10H)-one.

This 11(10H)-one derivative is treated with phosphorus pentachloride in toluene to yield 11-chloro-2-dimethylsulfamoyldibenz[b,f][1,4]oxazeipne. This 11-chloro compound is then heated with N-methylpiperazine in toluene containing pyridine as an acid acceptor to yield the desired 2-dimethylsulfamoyl-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine base, which yields with maleic acid in ethanol a maleate salt, mp 142—145°C., when recrystallized from acetone-ether.

EXAMPLE 20

Preparation of 2-Acetyl-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepin

p-(*o*-Aminophenoxy)acetophenone (Example 1) is treated, as described in Example 14, with phosgene in *o*-dichlorobenzene and cyclized with aluminum chloride to give 2-acetyldibenz[b,f][1,4]oxazepine-11(10H)-one.

Treatment of this 11(10H)-one derivative with one equivalent of phosphorus pentachloride in toluene yields the corresponding 11-chloro derivative which is heated with N-methylpiperazine in toluene to yield 2-acetyl-11-(4-methyl-1-piperazinyl)dibenz-[b,f][1,4]oxazepine, mp 116—118°C.

EXAMPLE 21

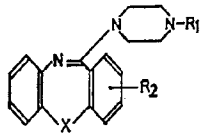
Preparation of 2-Dimethylsulfamoyl)-11-(4-methyl-1-piperazinyl)dibenzo[b,f]-[1,4]thiazepine

o-(*p*-Dimethylsulfamoylphenylthio)aniline (Example 6) is treated with phosgene in *o*-dichlorobenzene and cyclized with aluminum chloride to give 2-dimethylsulfamoyldibenzo[b,f][1,4]thiazepin-11(10H)-one.

This 11(10H)-one derivative is heated with phosphorus pentachloride in toluene to yield the corresponding 11-chloro derivative. Treatment of this with N-methylpiperazine in toluene containing pyridine then yields 2-dimethylsulfamoyl-11-(4-methyl-1-piperazinyl)dibenzo[b,f][1,4]thiazepine, mp 162—165°C.

WHAT WE CLAIM IS:—

1. A piperazine compound of the formula:



wherein X is oxygen or sulfur; R_1 is hydrogen, (C_1—C_4) alkyl, or hydroxy (C_1—C_4) alkyl; R_2 is cyano, di-(C_1—C_4) alkylsulfamoyl, (C_2—C_5) alkanoyl, α-chlorovinyl or (C_1—C_4) alkoxy carbonyl; or a non-toxic therapeutically useful acid addition salt thereof.

2. A compound according to Claim 1 except that R_2 is not (C_1—C_4) alkoxy carbonyl.

3. 2-Cyano-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine.

4. 2 - Dimethylsulfamoyl - 11 - (4 - methyl - 1 - piperazinyl)dibenz[b,f][1,4]-oxazepine.

5. 2-Acetyl-11-[4-(2-hydroxyethyl)-1-piperazinyl]dibenz[b,f][1,4]-oxazepine.

6. 2-Acetyl-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]-oxazepine.

7. 2-Acetyl-11-(4-methyl-1-piperazinyl)dibenzo[b,f][1,4] thiazepine.

8. 2-Acetyl-11-(1-piperazinyl)dibenz[b,f][1,4]oxazepine.

9. 2-Dimethylsulfamoyl-11-(4-methyl-1-piperazinyl)dibenzo[b,f][1,4]thiazepine.

10. 2-Dimethylsulfamoyl-11-(-1-piperazinyl)dibenzo[b,f][1,4]thiazepine.

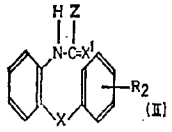
11. 2-(α-Chlorovinyl)-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine.

12. 2-Dimethylsulfamoyl-11-(1-piperazinyl)-dibenz[b,f][1,4]oxazepine.

13. 2-Dimethylsulfamoyl-11-(4-ethyl-1-piperazinyl) dibenz[b,f][1,4]oxazepine.

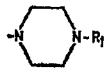
14. 11-(4-Methyl-1-piperazinyl)-2-propionyldibenz[b,f][1,4]oxazepine.

15. 2-Acetyl-11-(1-piperazinyl)dibenzo-[b,f][1,4]thiazepine.
16. 3-Cyano-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine.
17. 2-Ethoxycarbonyl-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine.
18. A method of preparing a compound as defined in Claim 1 or Claim 2, which method comprises
(a) cyclizing a compound of the formula:

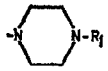


(II)

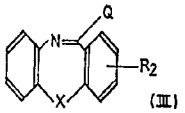
wherein X′ is sulfur or oxygen, Z is



or OH, halogen, OSO_2Ar, SH, SR, amino or substituted amino, wherein R_1, R_2 and X are as defined in Claim 1 or Claim 2, R is alkyl and Ar is aryl; and
(b) when required, before or after cyclization, converting Z from OH, halogen, OSO_2Ar, SH, SR, amino or substituted amino, into

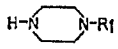


and
(c) when required, forming a non-toxic acid addition salt.
19. A method of preparing a compound as defined in Claim 1 or Claim 2, which method comprises
(a) reacting a compound of the formula

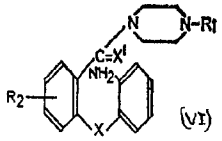


(III)

wherein Q is halogen, OH, OSO_2Ar, SH, SR, amino or substituted amino, wherein R is alkyl, Ar is aryl, and R_2 is as defined in Claim 1 or Claim 2, with a compound of the formula:



wherein R_1 is as defined in Claim 1 or Claim 2, and recovering the piperazine compound therefrom, and
(b) when required, forming a non-toxic acid addition salt.
20. A method according to Claim 19, wherein Q is (C_1—C_4) alkylamino or di-(C_1—C_4) alkylamino.
21. A method of preparing a compound as defined in Claim 1 or Claim 2, which method comprises
(a) cyclizing a compound of the formula



(VI)

wherein R_1, R_2 and X are as defined in Claim 1 or Claim 2, and X′ is oxygen or sulfur, and
(b) when required, forming a non-toxic acid addition salt.

22. A method of preparing a compound as defined in Claim 1 or Claim 2 substantially as hereinbefore described.

23. A compound as defined in Claim 1 or Claim 2, whenever prepared by a method according to any one of Claims 18—22.

24. A pharmaceutical preparation comprising a compound according to any one of Claims 1—17 or Claim 23 and a pharmaceutically acceptable carrier.

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